Can the experimental design for the screening of analgesic drugs be optimised?

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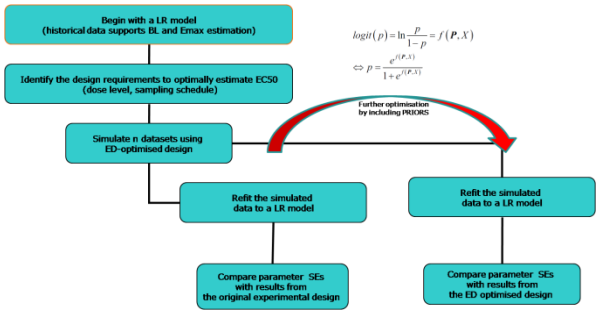
Introduction & Aim

Experimental models of pain show high variability in response, making it difficult to discriminate drug effect from noise. Given the limited experimental setting during drug screening, it is often not possible to explore the concentration-response relationships accurately. To that purpose, a logistic regression (LR) model is proposed to facilitate the comparison across compounds. Here we evaluated the feasibility of applying ED-optimality accounting for model and parameter uncertainty, with the objective of optimising dose and sample size in screening experiments. These concepts are illustrated for a paradigm compound.

Materials and Methods

Methods: The project concept is outlined in the flow chart hereunder.



$$logit(p) = \ln\frac{p}{1-p} = f(\boldsymbol{P}, X)$$

$$\Leftrightarrow p = \frac{e^{f(\boldsymbol{P},X)}}{1+e^{f(\boldsymbol{P},X)}}$$

We assumed drug potency (EC50), to be the parameter of interest during screening, with baseline effect and Emax as 'system properties' for truly positive compounds. Optimisation scenarios were based on feasibility, with limits for sample size, dose levels and sampling times. Experimental design variables are presented in Table 1.

Gabapentin data was used as example. Drug concentrations were simulated for the selected range of doses and sampling times using a two-compartment PK model (V2=0.18L, V3=3.8L, Cl=0.03L h^{-1}, Ka=0.6h^{-1}, Q=78L h^{-1}, F=0.83). The estimated EC50 from the original experiment was 208 ng ml^{-1} ,the Emax was 94.6 & the baseline was 3.4. POPED 2.10/ MATLAB 7.9 were used for the optimal design. Simulations were performed in NONMEM 6 and R 2.10 was used for graphical and statistical summaries.

Results

The model describing the original experimental data is presented in Figure 3. The optimised design variables are shown in Table 1.While in the original design, all subjects had the same sampling schedule, the optimised design envisaged a sampling window for each subject.

Model Type	Dose Level (Design variable 1)	Sample schedule (Design variable 2)	Sampling Windows
Experimental	0,30,100,300mg/kg (9 subjects per group)	0,1,2,3,4 hrs post dose	Nil
Optimal	0,62 mg/kg (range50-75mg/kg)- (12 subjects per dose group)	Gr1:0.254 (0.10-0.49), 5.487 (5-6), 5.508(5-6),9.487(9-9.998), 9.507(9.0-9.99)	0-0.5,5-6(2),9-10(2)
		Gr2:0.481(0.00-0.998),0.499(0.001-0.999),0.497(0.00-0.997), 7.489(7-8),7.494(7-7.999)	0-0.50(3),7-8(2)
		Gr3:0.494(0.00-0.999),0.499(0.00-0.998),0.499(0-0.999),7.490(7-7.998),7.497(7.001-7.999)	0-0.50(3),7-8(2)
		Gr4:0.484(0.00-0.998),0.484(0.00-0.998),0.500(0.002-0.998),7.495(7-7.999),7.504(7.000-7.998)	0-0.50(3),7-8(2)

The data simulated using the optimal design fitted the logistic regression model well, as can be seen from the response probability-concentration curves in fig 1.

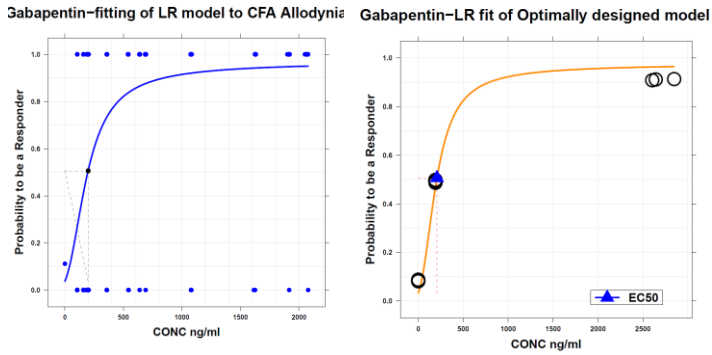
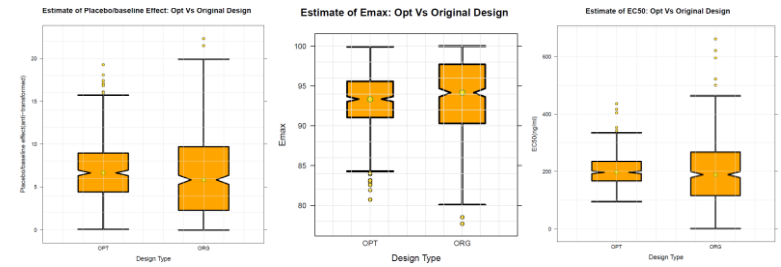


Fig1:model fitting for the original *versus* the optimised experimental design



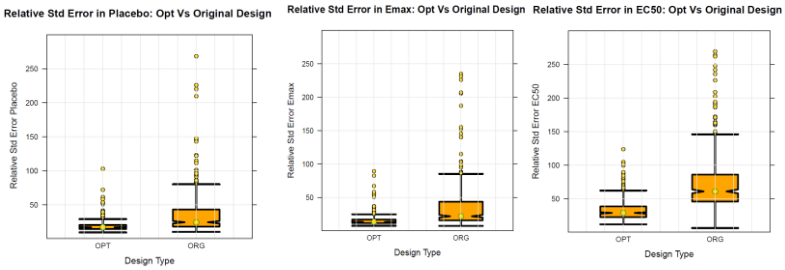


Fig 2: Comparison of baseline, Emax,EC50 and their RSEs for the original *versus* optimal design
The parameters are in the normal space and the RSEs in the logit space

Table2: Comparison of the parameter estimates and the corresponding relative standard errors (RSE) for the original and optimised designs.

Design Type	Baseline	RSE-baseline	Emax	RSE-Emax	EC50(ng/ml)	RSE-EC50
Original	3.10 (2.54e-11-14)	38.64 (81.25)	94.16 (77.71-100)	38.06 (57.18)	186.10 (0.924-661.20)	79.31 (123.28)
Optimal	3.66 (0.05-15.70)	18.50 (7.9)	93.35 (80.73-99.94)	15.53 (8.08)	197.69 (94.85-436.06)	32.33 (14.67)

For parameters median (range), and for RSEs mean (SD) presented

Discussion

Optimal design concepts can be used together with logistical regression modelling to facilitate the screening of compounds in pain research. This approach reduced the uncertainty around the parameter estimates as evidenced by RSE values. Here, we have presented the results of work in progress, wherein additional steps need to be implemented. Future efforts will focus on the optimisation of a single parameter , i.e., the primary variable of interest (EC50) in conjunction with the use of priors to support the estimation of baseline and Emax. In contrast to traditional experimental designs, for which accurate estimation of EC50 depends on observations between EC20 and EC80, a limited range of observations with multiple optimally designed sampling points may serve the same purpose. Further validation of the approach will be performed using additional data from an NCE.

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